Medical and Pediatric Oncology 26:166–172 (1996)

# Clinical Characteristics and Factors Affecting Growth in Long-Term Survivors of Cancer

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We evaluated clinical characteristics and growth in 51 (24 males) long-term survivors of childhood cancer (median follow up 12.7 years). Patients were shorter, had a higher proportion of body fat and higher systolic blood pressure than their controls. The change in relative height during treatment was −0.83 standard deviation score (S.D.S.) in patients with cranial irradiation and −0.32 S.D.S. in patients without cranial irradiation; the figures after treatment were −0.56 and 0.20 S.D.S., respectively. Half ($r^2 = 0.50$) of the variation in growth retardation during therapy could be explained by the cumulative doses of 6-mercaptopurine (6-MP) and vincristine and relative height at diagnosis. Cranial irradiation, increased relative height at diagnosis and young age at diagnosis were significant predictors of growth failure over the total observation period, explaining 43% of the variation.

We conclude that long-term survivors of childhood cancer have impaired linear growth, increased body fat mass and elevated systolic blood pressure. Young children who are tall for their age at diagnosis and treated with cranial irradiation have the highest risk of impaired growth after the diagnosis. High doses of 6-MP seem to contribute significantly to growth retardation during therapy. 

**Key words:** childhood cancer, acute lymphoblastic leukemia, solid tumor, growth retardation, obesity, follow-up studies

## INTRODUCTION

The past two decades have seen a dramatic improvement in the prognosis for children with cancer. At the same time the impact of long-term sequelae of the cancer therapy implemented has increased considerably. One of the harmful long-term effects of cancer treatment in childhood is growth impairment, which may be reflected in the quality of subsequent life.

Irradiation of the hypothalamic-pituitary axis (HPA) appears to be related to abnormalities in stature and physiologic growth hormone (GH) secretion [1,2]. The effect of irradiation is dependent on dose and fractionation [3,4]. The younger and taller the patient, the more pronounced the adverse effects on growth [5]. Other factors that may attenuate somatic growth include the disease itself, cytotoxic chemotherapy, malnutrition, corticosteroid therapy, recurrent infections, and emotional deprivation.

There is some indication that chemotherapy may have a separate effect on growth [6], but no detailed information is available on the effect of actual cumulative doses of individual chemotherapeutic agents. In this study we investigated current clinical characteristics in long-term survivors of childhood cancer. Another objective was to identify factors affecting growth impairment, with special emphasis on the cumulative individual doses of various chemotherapeutic agents.

## SUBJECTS AND METHODS

### Subjects

All living 59 subjects who had been treated for forms of childhood cancer other than brain tumors between 1972 and 1982 at the Department of Pediatrics, University of Oulu, were invited to participate in this study. We were unable to trace two survivors; one survivor was pregnant at the time of the study and three refused to participate in the study. One patient with Turner syndrome and one with Mulibrey nanism were excluded from the analysis. Accordingly, the final number of sub-

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Received March 21, 1994; accepted January 29, 1995.

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**TABLE I. Diagnosis, Sex Distribution, Age at Diagnosis and at Final Evaluation, and Total Follow-Up Time in Survivors of Childhood Cancer***

| Diagnosis | n (M/F) | Age at diagnosis (years) | Age at follow-up (years) | Follow-up time (years) |
|---|---|---|---|---|
| ALL | 29 (12/17) | 3.58 (0.30–14.04) | 17.52 (10.82–25.72) | 13.35 (8.94–18.63) |
| ANLL | 1 (1/0) | 8.58 | 18.94 | 10.36 |
| Wilms' tumor | 7 (3/4) | 3.59 (0.12–5.89) | 17.31 (10.50–24.62) | 12.30 (8.71–21.31) |
| Neuroblastoma | 3 (1/2) | 1.51 (0.94–2.16) | 15.77 (11.34–19.38) | 14.26 (10.40–17.22) |
| Lymphoma | 7 (4/3) | 12.72 (8.18–14.94) | 23.51 (19.14–26.41) | 11.25 (7.92–13.17) |
| Others | 4 (3/1) | 10.22 (9.15–11.88) | 23.82 (18.34–31.22) | 13.30 (8.98–20.15) |
| Total | 51 (24/27) | 4.20 (0.12–14.94) | 18.32 (10.50–31.22) | 12.68 (7.92–21.31) |

*Values are medians (ranges).

jects analyzed was 51, all of whom were pubertal (n = 27) or postpubertal (n = 23), except for one female. The diagnoses, sex distribution, age at diagnosis and at final evaluation, and follow-up time are shown in Table I. All patients were free from disease at the time of the follow-up. The median off-therapy time was 9.3 years (range 2.0–20.0 years). Six patients had been treated with chemotherapy, two with irradiation, and 43 with chemotherapy and irradiation. Thirty-two patients [26 acute lymphoblastic leukemias (ALLs), 4 lymphomas, 1 acute nonlymphocytic leukemia (ANLL) and 1 orbital rhabdomyosarcoma] had received radiation of the HPA (range 10–46 Gy), 13 (12 leukemias and 1 lymphoma) to the testis (24 Gy), and 14 (7 Wilms' tumors, 3 neuroblastomas, 3 ALLs and 1 histiocytoma fibrosum) to the region of the trunk (range 6–52 Gy). Cranial irradiation was given in 10–17 fractions of 1.5–2.0 Gy each over 14–33 days in patients with ALL with a total dose of 15–25 Gy. Testis irradiation was given in 12 fractions of 2.0 Gy each over 16 days. Five survivors had been started on GH therapy, and their growth data were included in the analysis up to the end of cancer treatment. Nine subjects were on testosterone and two on thyroxin supplementation. One female took estrogen pills for irregular menses. All patients receiving GH responded with an increase in their growth velocity.

Systemic induction therapy for leukemia comprised vincristine, prednisolone and doxorubicin. Maintenance therapy included daily doses of 6-mercaptopurine (6-MP) and weekly doses of methotrexate and cyclophosphamide. During remission, reinductions with vincristine, doxorubicin and prednisolone were given for one week each month. Central nervous system (CNS) prophylaxis included cranial irradiation and 6–8 intrathecal injections of methotrexate. Radiation therapy was started 5–6 weeks after the diagnosis when the systemic induction therapy was completed and the patient was in remission. Testicular radiation continued immediately after CNS irradiation. Maintenance therapy was completed after a relapse-free period for 3 years. Two subjects were in second remission at the time of the follow-up. The treatment for solid tumors comprised surgery, local radiation, and cytostatic therapy, which included vincristine, actinomycin-D, cyclophosphamide, and dacarbazine. The patient with abdominal lymphoma was treated according to a modified ALL protocol.

The control group consisted of 51 healthy age- and sex-matched subjects recruited from a public or medical school. One of them was prepubertal, 16 were pubertal and 34 were postpubertal. These subjects had no history of chronic diseases or abnormalities on physical examination. None of the controls had any chronic medication.

## Methods

All subjects were examined at the final evaluation by the same doctor (K.K.T.). Earlier growth data were collected retrospectively. Actual height was measured with a Harpenden stadiometer, and the subjects were weighed on an electronic scale. The individual heights and weights reported represent the average of three separate measurements. Relative height was estimated from growth charts for Finnish children [7] and expressed as standard deviation scores (S.D.S.). Relative weight was calculated from the subject's actual weight divided by the expected weight for height and multiplied by 100. The results were expressed as a percentage, with 100% representing the mean value for height. Obesity was defined as a relative weight exceeding 120%. The stage of puberty was assessed using the criteria of Tanner and Whitehouse [8]. Midparental height S.D.S. was calculated according to the following formula: [(mean of parents' height in cm − 171 cm)/10] S.D.S. [9]. The target height deficit (THD) was assessed by subtracting the relative height at the time of the final evaluation from midparental height S.D.S. Changes in relative height were assessed for three time periods: (1) from diagnosis to completion of chemotherapy, (2) during off-therapy, and (3) from diagnosis to last follow-up. Triceps and subscapular skinfold thicknesses were measured with a Harpenden skinfold caliper (John Bull, British Indicators Ltd., St. Albans, Herts, UK) [10]. In subjects younger than 18 years, body density was calculated from the combined results of triceps

**TABLE II. Anthropometric and Clinical Measurements in Patients and Controls†**

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Patients n = 20 | Controls n = 20 | *P** | Patients n = 26 | Controls n = 26 | *P** |
| Relative height at diagnosis (S.D.S.) | −0.06 (0.79) (n = 23) | — | — | −0.10 (1.09) (n = 26) | — | — |
| Current height (cm) | 171.8 (8.2) | 176.4 (6.8) | 0.026 | 155.4 (9.1) | 161.4 (8.6) | 0.006 |
| Current relative height (S.D.S.) | −0.61 (1.14) | 0.11 (1.04) | 0.03 | −1.09 (1.29) | −0.15 (1.10) | 0.01 |
| Target height deficit (S.D.S.) | 0.23 (1.00) | — | — | 1.05 (1.08) | — | — |
| Absolute sitting height (cm) | 89.9 (5.4) | 92.6 (3.5) | 0.04 | 82.3 (5.6) | 86.0 (5.1) | 0.002 |
| Relative sitting height (%) | 52.4 (1.4) | 52.6 (0.8) | 0.66 | 52.9 (1.2) | 53.3 (1.4) | 0.15 |
| Relative weight at diagnosis (%) | 99 (11) (n = 23) | — | — | 100 (9) (n = 26) | — | — |
| Current weight (kg) | 68.3 (19.8) | 68.2 (11.1) | 0.98 | 52.4 (12.1) | 52.1 (11.3) | 0.89 |
| Relative weight (%) | 116 (26) | 110 (15) | 0.35 | 115 (17) | 102 (15) | 0.004 |
| Body fat mass (%) | 21.0 (7.5) | 16.6 (4.4) | 0.02 | 30.1 (5.1) | 24.4 (5.3) | <0.0001 |

†Values are means (S.D.).
**P*-values are from the Student's paired two-tailed t-test.

and subscapular skinfold thicknesses as described by Parizkova [11]; for older subjects the method of Durnin and Womersley [12] was used. Body fat mass was then calculated using the equation of Keys and Brozek [13]. Blood pressure was measured with an ordinary mercury sphygmomanometer (Instru Trimline, Instrumentarium, Finland) from the right arm after a minimum rest of 20 minutes with an inflatable cuff which covered at least two thirds of the area of the upper arm. The subject's arm was on the table to avoid artefacts due to the position of the arm [14]. Blood pressure was rounded to the nearest even number of mm Hg. Systolic pressure was measured to Korotkoff's 1st phase, and diastolic pressure to Korotkoff's 5th phase. Patient charts were reviewed on a daily basis to collect data on medication and irradiation. The calculated cumulative doses of chemotherapeutic agents were divided by the body surface area at the end of therapy. Bone age was evaluated from a radiograph of the left hand and wrist according to the criteria of Greulich and Pyle [15]. Relative bone age was assessed in those (10 males and 10 females) with unfused epiphyseal lines.

### Statistical Analysis

Descriptive data are given as medians and ranges or means and standard deviations (S.D.). Distributions were analyzed with cross-tabulation and Chi-square statistics. Differences between various time points and between the patients and their age- and sex-matched controls were analyzed with the Student's paired two-tailed t-test, and subgroup analyzes with the Student's unpaired two-tailed t-test. Linear regression analysis was used for correlation analyses and multiple stepwise regression analysis for identifying factors explaining the variation in growth impairment during various time periods. Age at diagnosis, relative height and weight at diagnosis, sex, the dose of cranial irradiation, individual cumulative doses of all used anti-neoplastic agents, and duration of therapy were included in each multiple regression model. A *P*-value less than 0.05 was considered significant.

## RESULTS

### Patients vs. Controls

The 51 long-term survivors of childhood malignancies were studied after a median follow-up period of 12.7 years (range 7.9–21.3 years). Patient characteristics are summarized in Table I. Anthropometric and clinical measurements of both patients and controls are shown in Table II.

In the whole patient group, both males and females

**TABLE III. A: Changes in Relative Height During Therapy**

| Sex | Cranial irradiation n = 32 mean (S.D.) | No cranial irradiation n = 17 mean (S.D.) | *P** |
|---|---|---|---|
| Male (n = 16/7) | −0.79 (0.40) | −0.33 (0.60) | 0.04 |
| Female (n = 16/10) | −0.88 (0.69) | −0.32 (0.51) | 0.04 |
| *P*** | 0.65 | 0.97 | |

**TABLE III. B: Changes in Relative Height During Off-Therapy**

| Sex | Cranial irradiation n = 27 mean (S.D.) | No cranial irradiation n = 18 mean (S.D.) | *P** |
|---|---|---|---|
| Male (n = 12/7) | −0.16 (0.66) | 0.26 (0.83) | 0.25 |
| Female (n = 15/11) | −0.88 (0.66) | 0.17 (0.68) | 0.001 |
| *P*** | 0.01 | 0.81 | |

**TABLE III. C: Changes in Relative Height From the Time of Diagnosis to the Final Evaluation**

| Sex | Cranial irradiation n = 27 mean (S.D.) | No cranial irradiation n = 17 mean (S.D.) | *P** |
|---|---|---|---|
| Male (n = 12/7) | −0.92 (0.57) | −0.07 (0.80) | 0.01 |
| Female (n = 15/10) | −1.81 (0.90) | −0.16 (0.76) | <0.001 |
| *P*** | 0.006 | 0.82 | |

*Student's unpaired two-tailed t-test; cranial irradiation ±.
**Student's unpaired two-tailed t-test; male/female.

had a reduced relative height compared to their controls. In absolute terms, the adult males (bone age ≥19 years, n = 10) were on an average 2.5 cm and the adult females (bone age ≥17 years, n = 16) 5.4 cm shorter than their controls. Five out of 26 adult survivors (19%) had a relative height below −2 S.D.S. Adult females had a more severe THD than adult males (1.20 S.D.S. vs. 0.02 S.D.S.; $P = 0.02$). Absolute sitting height was lower in both male and female patients than in controls, while relative sitting height was almost the same.

Absolute weights were also of the same magnitude in patients and controls. Female patients had a higher relative weight than their controls. Sixteen (35%) patients were obese, while seven (15%) control subjects ($P = 0.03$) met the criterion of obesity (relative weight >120%). There was a significant increase in relative weight from the time of diagnosis to the final evaluation [mean (S.D.), 100 (10)% vs. 115 (21)%; $P < 0.0001$]. Both male and female patients had an increased body fat mass compared to their controls. Relative bone age was equal in ten males and in ten females still growing [mean (S.D.), −0.1 (0.8) S.D.S. vs. 0.1 (1.3) S.D.S.]. Relative bone age was lower than −2 S.D.S. in 1 out of 20 patients (5%), while none had a bone age exceeding +2 S.D.S. Systolic blood pressures were higher in patients than in their controls [mean (S.D.), 124 (13) mm Hg vs. 119 (12) mm Hg; $P = 0.01$]. Diastolic blood pressures were similar [mean (S.D.), 70 (10) mm Hg vs. 70 (9) mm Hg] in both groups.

## Changes in Relative Height During Different Time Periods

Patients treated with cranial irradiation showed a more marked reduction in relative height during treatment than nonirradiated patients (Table III). Following the completion of therapy, the nonirradiated patients experienced catch-up growth, whereas relative height continued to decrease in children with cranial irradiation. Among those who had received cranial irradiation, growth impairment was more severe in females than in males during off-therapy time. The total decrease in relative height was greater in subjects with cranial irradiation, and females were more heavily affected in this group.

## Factors Affecting Growth

Multiple stepwise linear regression analysis demonstrated that it was possible to explain half ($r^2 = 0.50$) of the variation in growth during therapy by including the individual cumulative dose of 6-MP (partial standard coefficient −0.47; $P < 0.001$), relative height at diagnosis (partial standard coefficient −0.30; $P = 0.01$) and the cumulative dose of vincristine (partial standard coefficient −0.29; $P = 0.04$) as predictors. A small proportion ($r^2 = 0.14$) of the variation in growth impairment during off-therapy could be explained with the dose of cranial irradiation ($P < 0.01$). Analyzing the variation in growth failure over the total observation period, 43% ($r^2 = 0.43$) was explained by the dose of cranial irradia-

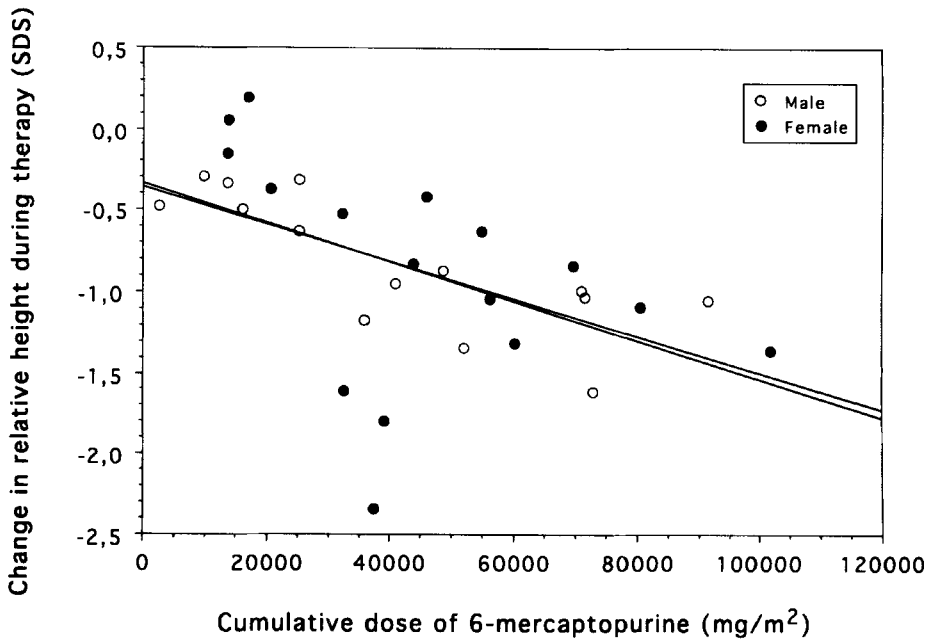


**Fig. 1.** Correlation between individual cumulative doses of 6-MP and changes in relative height during therapy in cranially irradiated males ($y = -0.354 - 1.147 \cdot 10^{-5} \cdot x$; $r = -0.78$; $P = 0.001$) and females ($y = -0.335 - 1.204 \cdot 10^{-5} \cdot x$; $r = -0.43$; $P = 0.09$).

tion ($P < 0.001$), relative height at diagnosis ($P = 0.01$) and age at diagnosis ($P = 0.01$).

Most patients who were treated with 6-MP suffered from ALL. To clarify the role of cumulative doses of chemotherapy, this subgroup was analyzed separately. Close to 40% ($r^2 = 0.39$) of the variation in growth impairment during therapy could be explained by relative height at diagnosis ($P = 0.01$) and cumulative dose of 6-MP ($P = 0.03$) in the ALL patients, while the dose of cranial irradiation ($P = 0.01$), relative height at diagnosis ($P < 0.01$) and sex ($P = 0.02$) explained 39% ($r^2 = 0.39$) of the variation in growth retardation during the total observation period in this group. Among patients treated with cranial irradiation, there was a stronger correlation between the change in relative height during treatment and cumulative dose of 6-MP in males ($r = -0.78$; $P = 0.001$) than in females ($r = -0.43$; $P = 0.09$; Fig. 1).

## DISCUSSION

This study indicates that in survivors of childhood cancer, growth impairment may be a more prominent phenomenon during than after therapy. This observation may, however, not be permanent, since all patients studied had not reached their final height. A recent study has reported a late decrease in relative height in long-term survivors of ALL [16]. In patients with no history of cranial irradiation, there even seems to occur catch-up growth following completion of therapy. We observed that higher cumulative doses of 6-MP and vincristine contributed significantly to the retardation of linear growth during therapy. A third factor predisposing to slow linear growth during treatment was high relative height at diagnosis. About half of the variation in growth impairment during therapy could be explained by these three factors.

Our findings on posttreatment growth were consistent with expectations: the most significant factor predisposing to growth failure was the dose of cranial irradiation. The dose of cranial irradiation, relative height at diagnosis and age at diagnosis turned out to be significant predictors of growth retardation during the total time period. According to the multiple regression analysis, sex had no major impact on the degree of growth impairment during that time. On the other hand, adult females showed a more prominent THD than males. These observations appear to conflict with each other, but the discrepancy can be explained by the fact that in this study the girls were younger at diagnosis than the boys [mean (S.D.), 4.4 (3.1) years vs. 7.1 (4.7) years; $P = 0.02$] and age at diagnosis was a stronger predictor of retarded growth than sex in the multiple regression analysis. In other words, this survey confirms previous studies in its observation that increasing doses of cranial irradiation, young age and tall stature at diagnosis appear to make the child more prone to subsequent growth failure [6,17].

The female patients in the present study experienced

their menarche at a mean age of 11.9 years, that is, on an average 1.3 years earlier than in healthy Finnish girls (13.2 girls) [18]. In females with ALL, menarche occurred at a mean age of 11.6 years. Early menarche is a recognized consequence of cranial radiation [19,20] and it results in an early fusion of the epiphyseal centres with the appropriate long bones. Accordingly, early menarche at least partly explains the pronounced THD in female survivors of childhood cancer.

In this study the cumulative doses of various chemotherapeutic agents and corticosteroids were estimated retrospectively from the patients' charts and may therefore include some inaccuracies. There was considerable interindividual variation in the cumulative doses, and in many cases the actual doses differed markedly from assumed levels. This was obviously due to the fact that treatments were individually modified according to changes in the white blood cell count and episodes of infections. The association between cumulative doses of 6-MP and vincristine on the one hand and impaired growth during treatment on the other, must in any case be interpreted with caution and should be confirmed in prospective longitudinal studies. Nevertheless, these observations suggest that more attention should be paid to cumulative doses of individual chemotherapeutic agents when analyzing the relationship between cytotoxic chemotherapy and growth in children with cancer.

At this point our comments on the growth-retarding mechanisms of 6-MP and vincristine remain speculative. Since 6-MP is an antimetabolite, growth impairment during treatment may be the result of a general antimetabolic effect. In addition, it has been shown that GH-stimulated hepatic production of somatomedin activity is profoundly depressed by 6-MP and vincristine in vitro [21]. GH action is largely mediated by insulin-like growth factor-I (IGF-I, previously named somatomedin C), and a substantial proportion of circulating IGF-I derives from the liver. The combined use of several antimetabolic agents including 6-MP and methotrexate might cause hepatic fibrosis [22,23] which could result in reduced hepatic synthesis of IGF-I and decreased circulating IGF-I concentrations. This could then be reflected in impaired linear growth. We were unable to find any relationship between cumulative doses of prednisolone and growth impairment during or after therapy. This finding suggests that the corticosteroid dose does not play a significant role in the evolution of impaired linear growth in survivors of childhood cancer.

The decrease in relative height was significantly greater in those subjects treated with cranial irradiation than in the nonirradiated children even during therapy. In subjects treated with cranial irradiation, the average change during the total study period was −1.32 S.D.S. In adult survivors of ALL the change (−1.50 S.D.S.) was of the same magnitude as reported earlier [24–28].

Both male and female patients had a higher mean relative weight than their controls, although the difference was significant only in females. Both sexes had an increased portion of body fat, and about one-third of the patients were obese. This proportion is considerably higher than in the study of Zee et al. [29], who reported an 8% prevalence of obesity at 5 years after cessation of therapy in survivors of childhood ALL when the criterion was a body mass index exceeding the 95th percentile. There may be several factors contributing to an increased body fat mass in this patient population, such as abnormal secretory dynamics of the HPA after radiation, reduced GH secretion, and decreased physical activity. Whatever the causes are, the increased proportion of body fat raises the important issue as to whether long-term survivors of childhood cancer are more predisposed than the general population to the metabolic syndrome characterized by obesity, hyperlipidemia, hyperinsulinemia, hypertension and enhanced risk of Type 2 diabetes and cardiovascular disease [30]. The present observation of a significantly higher systolic blood pressure in patient than in controls would appear to lend support to such a hypothesis. If this is true, it might have an impact on the long-term prognosis of survivors of childhood cancer. This possibility remains to be explored in future studies.

## CONCLUSIONS

According to the present study a child who is young and tall for age at the diagnosis of cancer and who is treated with cranial irradiation and high cumulative doses of 6-MP, runs the highest risk of impaired growth after the diagnosis. In addition, long-term survivors of childhood cancer have increased body fat mass and systolic blood pressure, which may predispose these individuals to an enhanced risk of the metabolic syndrome associated with increased morbidity and mortality at older age.

## ACKNOWLEDGMENTS

This research was supported by the Fund for Children's Cancer, Oulu University Central Hospital, the Alma and K. A. Snellman Foundation, Oulu, Finland (K.K.T.), and the Sigrid Jusélius Foundation, Helsinki, Finland (M.K.).

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